Ethics and International Collaborative Research

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Disclaimer

- The opinions expressed are the author's own. They do not reflect any position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services

International collaborative research

- Protocol that involves at least two countries
  - Sponsor country pays, host country site
  - Two sites
- On health problem in host country
  - Malaria, HIV or
- Increasingly, “Outsourcing”

Special concerns

- Different regulations
  - Children
  - Emergency Research
  - Informed consent requirements
- Different scientific judgments
  - Acellular pertussis vaccine trials
- Different cultural traditions
  - Individual informed consent

1. Economic differences

- 1. Standard of care issues. Choice of trial design interventions
- 2. Ancillary care issues
- 3. Post-trial benefits
  - To trial intervention
  - To ancillary care provided
- 4. Responsiveness to health needs requirement

1. Trial design interventions

- What interventions should be provided as part of the design of the study
  - What should be provided in the control arm
  - What study intervention should be provided
- Easy answer: You provide the two interventions that you wish to compare
- What about placebo in control arm when there is a standard treatment available

1. Placebo use

- Accepted under following conditions
  - If it is necessary for scientific reasons
    - Variability in response to standard interventions
  - Denying participants standard interventions does not expose them to serious harm
    - Disagreement about what constitutes serious harm
      - Antihistamines for runny nose vs.
      - Antidepressant drugs

1. Economic issues

- In resource poor settings the same presumption holds: If there is a standard intervention, that should be provided in the control arm
- Problem arises when there is an effective intervention that cannot be provided to most people in host country for economic reasons
- This could make trial irrelevant for host country health problems

1. Exception

- Many will therefore allow exceptions. Two conditions:
  - Scientifically necessary
  - In order to obtain results useful for country where trial takes place
- Others, notably the Declaration of Helsinki, maintains that one should NOT allow this exception

1. Examples

- Test a simplified diagnostic method to monitor effect of HIV treatment to take the place of viral load measurements
- Test interventions that will prevent HIV infection during breastfeeding, without bottle feeding
- Examples such as these show that exceptions are necessary

2. Ancillary care examples

- Treatment that is provided for study participants that is NOT necessary for the design of the study
  - Identification of conditions that need treatment during screening and study visits
  - HIV treatment in a malaria vaccine trial
  - HIV treatment in a study of malaria pathogenesis in children
  - Malaria treatment in a study of malaria pathogenesis

2. Guidance

- CIOMS: Although sponsors are, in general, not obliged to provide health care services beyond that which is necessary to conduct research, it is morally praiseworthy to do so

2. Ancillary care: current status

- No obligation to provide ancillary care during trial
- Many researchers do provide some amount of ancillary care
- Under-explored topic
- Belsky & Richardson have attempted to derive a limited obligation based on an entrustment model, rather than a “Good Samaritan” type obligation

3.1. Post-trial access to study intervention

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by that study
  - Helsinki-2000
- Only an obligation to provide study interventions, not ancillary care interventions, after trial is completed

3. 1. Acute versus chronic conditions

- Post-trial access to study intervention is usually not a problem for acute conditions
- Not a problem to provide effective vaccine to control group
- Problem arises for
  - Continued treatment for chronic conditions when there is a potential for long term financial and logistical commitment

3. 2. Post-trial access to ancillary care

- Long term access to care for conditions identified during a vaccine trial
  - Treatment for HIV identified during screening phase in malaria vaccine trials or in HIV vaccine trials
  - Treatment for those who seroconvert during HIV preventive trials
  - Treatment for other chronic conditions identified during vaccine trials

3. Lack of guidance

- Almost no guidance regarding long term post trial obligations
- Even if there is provision for referral to national system of treatment, the system will probably provide a lesser standard of care than that which was available in the trial
- Question therefore also is whether there is an obligation to ensure state of the art care

3. NIH ARV Guidance

- For antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment
- Applicants are expected to provide NIH Program Staff for evaluating their plans that identify available sources, if any, for provision of antiretroviral treatment to research participants
- Priority may be given to sites where sources are identified for provision of ARV treatment

3. Conclusions

- At a minimum researchers should address the issue of post trial access to care and treatment
- ERCs should NOT require guaranteed access (legally binding agreement, money in the bank)
- Need to work out examples of successful strategies
  - Streamlined referral processes
  - Specific conditions covered by specific sponsors of trials

4. Responsiveness

- Current Helsinki: Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research

4. Post trial availability to general community

- CIOMS: As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to the inhabitants of the underdeveloped community in which the research was carried out. Exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun

4. Criticism of reasonable availability

- Narrow view of benefits
- Not applicable to much research
  - Phase I trials
  - Observational studies
- It may be an explicit policy choice to decide to do a trial that will provide needed expertise to do future, more relevant trials
  - Hepatitis A vs. HIV vaccine trials in Thailand

4. Fair benefits framework

- All benefits and risks need to be evaluated
  - Benefits and risks to research participants
  - Benefits to general community during trial
  - Benefits after the completion of the trial
- Community involvement
  - Involvement at all level of decision making
  - Uncoerced
- Transparency in decision making

4. Controversy

- Fair benefits framework has been criticized because it provides a minimalist view of researcher obligations
- But it was intended to get away from the narrow view of reasonable availability, arguing that there are other types of benefits of research that sometimes may be important

Three cases

- HIV treatment trial in South Africa
- Blood pressure trial in India
- Malarone prevention trial in Indonesia

HIV treatment trial in SA

- Pharmaceutical company wants to do a treatment trial of a new promising drug combination
- Ethics committee requires that those who benefit receive the drug combination as long as they benefit afterwards
- Company says no: it is too costly, partly because they have to buy rival company drugs
- Activist community wants the trial

Blood pressure trial in India

- Pharmaceutical company wants to do a trial of a new blood pressure drug in India. A new version of an existing drug whose safety profile is well established
- They want to do it India because it is $200 m cheaper to do it there
- Drug will be sold almost exclusively in Western Europe and North America

Malarone trial in Indonesia

- Trial to establish the effect of malarone on prevention of malaria
- Proposed for a malaria endemic region of Indonesia.
- Placebo controlled trial. Observe number of malaria cases in the two groups
- Number of safety measures in place
- Community wants it because of health benefits